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NIH Environmental Health Prevention Research

Statement of

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Madam Chairman and Members of the Committee,

I am pleased to appear before this distinguished panel to discuss the possible connections between the environment and human health.

GENE-ENVIRONMENT INTERACTION . . . THE CENTERPIECE FOR DISEASE PREVENTION

Prevention of disease has proven to be the most cost-effective means of reducing health care costs. This past century saw tremendous increases in health and longevity because of water sanitation, vaccinations, refrigeration and regulation of food safety. The new century will see further improvements as we identify and implement national prevention strategies based on knowledge of gene-environment interactions.

Although most of the visible environmental problems of the 1950s and 1960s have been ameliorated, massive quantities of toxic agents are still polluting our environment. This includes chemicals that are known to be rodent and human carcinogens and neuro-, immuno-, or developmental toxins. Whether current levels of exposure to these agents are contributing to the high or increasing incidence of cancer, Parkinson's and Alzheimer's Disease, asthma, autism, learning disabilities, diabetes, or other complex disorders is a matter of considerable concern. Finding answers to these questions has been a slow and difficult process. The traditional methodologies available to environmental health researchers have not been adequate to elucidate the intricate gene-environment interactions involved in the development of complex diseases.

Most chronic diseases, including those mentioned above, arise from the complex

interactions between genes and environmental factors. (By environmental factors, I mean anything in the environment that might be ingested, inhaled, or absorbed through the skin.) The relationship between genes and the environment can be compared to a loaded gun and its trigger. A loaded gun by itself causes no harm; it is only when the trigger is pulled that the potential for harm is released. Genetic susceptibility creates an analogous situation where the loaded gun is one or a combination of susceptibility genes and the trigger is an environmental exposure. One can inherit a predisposition to have a disease, but never have the disease unless exposed to the environmental trigger(s). Therefore, most chronic diseases cannot be prevented until both the genetic and environmental contributions to their development are elucidated. Unfortunately, the relationship between genes and the environment is not yet well understood nor extensively studied. In the past, limited knowledge of human genetics hampered progress in this area. But, with the recent publication of the map of the human genome, the opportunity now exists (1) to determine how genetics, age, and stage of development influence susceptibility to disease from environmental exposure; (2) to assess the toxicity of the thousands of environmental agents to which humans are exposed; and (3) to develop approaches for the direct measurement of human exposure. The information generated by such studies is critical for preventing illnesses caused by environmental triggers.

Identification and modulation of the effects of environmental triggers are promising targets of opportunity for prevention. Thus, the National Institute of Environmental Health Sciences (NIEHS) has developed several new initiatives to achieve these objectives. This information promises to provide the next generation of public health prevention

strategies, moving us beyond water disinfection and vaccines into an era where genetic information and environmental data can be used to prevent major diseases and disabilities.

Unfortunately, the exploration of the relationship between genes and the environment has been hampered in the past by the use of the most simplistic models to study human disease; that is, diseases are caused by mutations in single genes or by exposure to a single environmental agent. Rarely in the past were interactions between multiple genes or between genes and environmental factors investigated as causes of human illnesses. While the "single-factor" approach has led to the successful identification of many susceptibility genes and environmental risk factors, understanding of many chronic diseases and development of prevention strategies are still elusive.

The relative contribution of genes versus the environment to human illness has been debated for decades. A role for environmental exposures is supported by geographic differences in incidence of disease, by variation in trends over time, and by studies of disease patterns in immigrant populations. Also, population-based, twin-cohort studies, the "gold standard" for distinguishing between the contribution of genetics versus the environment, suggest that the environment plays a prominent role in disease development. However, spectacular developments in gene discovery over the past 15 years, combined with the tremendous publicity surrounding the Human Genome Project, have led to confusion and false expectations in the minds of the general public about the relative risk of environmental and genetic factors.

A recent landmark report by Lichtenstein, et al., comparing the incidence of cancer in unrelated individuals, identical twins, and non-identical twins, found that genetics

accounted for only approximately one-third of the risk for developing ten of the most common cancers, and that environmental factors accounted for the preponderance or two-thirds of the risk (Lichtenstein et al, *New England Journal of Medicine* 343: 78, 2000). The authors concluded that: "Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms and that the environment has the principal role in causing sporadic cancer." Similar results have been obtained for other diseases. For example, twin studies have shown that environmental triggers account for the majority (~85%) of late-onset (after age 50) cases of Parkinson's Disease (Tanner et al, *Journal of the American Medical Association* 281: 341, 1999) and about two-thirds of autoimmune diseases (Powell et al, *Environmental Health Perspectives* 107: 667, 1999).

Given that most chronic illnesses are caused by gene-environment interaction, knowledge of one should increase our understanding of the other. For example, information about environmental risk factors should point to genes that might modify the risk, and identification of susceptibility genes should help identify previously unrecognized environmental risk factors. Also, if genes and the environment interact to generate risk greater than each acting alone, then eliminating either the genetic or the environmental influence represents an effective strategy for disease prevention. Clearly, it is time that we move beyond the nature versus nurture debate, and exploit scientific opportunity to improve human health.

By integrating two currently divergent fields - genomics and toxicology, one can investigate gene-environment interaction to generate information necessary to prevent or cure cancer and other chronic diseases. To exploit these technologies to prevent the

existing epidemic of disease, NIEHS has targeted three critical areas of research: (1) identification of the suite of gene-environment interactions involved in the development of the major diseases, (2) development of public health or medical prevention/intervention strategies, and (3) development of mechanisms to translate knowledge and technology into the practice of preventive and clinical medicine. By investing in these areas of research, NIEHS expects to be a major contributor to one of the most important functions of government - the protection of human health.

INFORMATION GAP IN UNDERSTANDING GENE-ENVIRONMENT INTERACTIONS

Carcinogenicity and Toxicity Assessment: Estimates are that 70-75% of the high-volume, high-use chemicals in commercial use in the United States have not been assessed for human toxicity (National Academy of Sciences, 1980; Environmental Defense Fund, 1993). While many of these, if not most, may not require testing since they are very similar to chemicals already tested, a substantial number do need more testing. However, given the sheer magnitude of the problem, we can never satisfy this testing requirement using traditional technologies. Without faster and cheaper test systems than the traditional rodent bioassays that can take five-seven years to complete and cost $2-6 million per chemical, we will continue to lack needed data. One promising approach is to harness the technological advancements made through the Human Genome Project into new ways to assess environmental agents for carcinogenicity and toxicity. To this end, NIEHS

developed the National Center for Toxicogenomics in November 2000 to promote the use of three new technologies (genomics, proteomics and metabonomics) to develop more efficient and cost-effective toxicity/carcinogenicity screening methods (Science 289: 536, 2000; New York Times, November 28, 2000).

<u>Susceptibility to Environmental Exposures</u>: Throughout life, human and other organisms are subjected to environmental insults on a continual basis. As a result, sophisticated metabolic pathways have evolved to buffer against toxic injury. Collectively, these buffering pathways or mechanisms have been referred to as the "environmental response machinery." All human genes, including those that code protein components of the environmental response machinery, are subject to genetic variability that can result in outright failure or altered efficiency in a buffering or protective mechanism.

Although reference is made to the human genome, the concept of a single genome is misleading. Each individual's genetic makeup, with the exception of identical twins, is unique. While the genome of individuals are 99.9% identical, the 0.1% variation leaves considerable room for individual differences among the approximately three billion nucleotide base pairs that make up the human genome. The variation in gene structure among individuals is known to play a significant role in disease development by increasing or decreasing sensitivity to environmental insults.

To date, very few environmental susceptibility genes have been identified, but with improvements in methods of gene discovery and genotyping, large-scale studies of the genetic basis for susceptibility to environmental exposures are now practical. Therefore,

NIEHS initiated a search for such environmental susceptibility genes approximately three years ago with the announcement of the Environmental Genome Project (Science 278: 569-570; Nature Genetics 18: 91-93), by contracting with the genome sequencing laboratories developed by the Human Genome Project. The questions being addressed by the genome discovery project include: (1) Which of the genes, coding for proteins involved in buffering against environmental insults, vary structurally among individuals, (2) What is the relative distribution of the various forms of the genes in the U.S. population, and (3) What are the consequences of the genetic alterations with respect to toxic injury or susceptibility to environmental exposures? To date, we have completed the search for functional variations in 104 of the 544 genes initially targeted for analysis. This has been done in a sufficient population sample size so that we can be reasonably certain that variations discovered are representative of the U.S. population.

I should also emphasize that genes are not the only factors that contribute to differences in susceptibility to environmental exposures; age or stage of development, behavior, general health or nutritional status, gender, and socio-economic status can have a spectacular influence. In the interest of time, these issues will not be addressed here, but they are among the top investment priorities of the NIEHS. For example, NIEHS and EPA have developed twelve Children's Environmental Health and Prevention Research Centers to address the unique susceptibilities of children.

Assessment of Exposure: Little is known about actual human exposure and body burdens of environmental pollutants. This knowledge gap hampers regulatory decision

making and introduces uncertainties in setting exposure limits. It also limits our understanding of dose-response relationships and capacity to develop effective prevention strategies. Exposure is typically estimated using indirect surrogates of environmental quality, such as toxic release and production inventories and environmental monitoring. Actual exposure is highly variable for individuals and subpopulations; it is really a function of individual uptake, metabolism, excretion, and behavior. So the assumption that all men, women, and children living in the same geographic area have similar exposure is seriously flawed. What we need are direct measures of exposure based on tissue analysis or deposition. Simple monitoring of levels of chemicals in the environment does not necessarily reflect amounts taken up and deposited in tissues. NIEHS is developing new genomic tools to strengthen this area of human risk assessment. This information is important for epidemiologic or population based studies to identify risk factors for disease.

Improved exposure assessment and a national database for tracking diseases are two areas that I, as Director of the NIEHS, want to address to improve environmental health research. A better understanding of the actual, real-world exposures of our citizenry will enable environmental health scientists to use this information to set priorities for what toxicity studies need to be done first. A disease tracking system that could be overlaid with exposure assessment data, would allow us to identify potential environmental triggers of disease. This information would suggest hypotheses that could be pursued in laboratory studies to better define the link between environment and disease and to identify the critical pathways of disease induction.

The NIEHS teamed with the Centers for Disease Control and Prevention (CDC) to

assess actual exposures in a representative set of U.S. citizens to common endocrine disrupting compounds arising from plastics. This information showed surprisingly high levels of exposure to certain compounds that had a relatively low production volume. The NIEHS used these results to initiate studies on the possible health effects of these exposures. In the absence of the exposure assessment information generated by the CDC/NIEHS collaboration, we would have given a lower priority to some of these chemicals because of the presumption that the population did not have significant exposures.

The NIEHS is also a partner with the National Institute of Child Health and Human Development (NICHD) to create a National Children's Study. Authorized by the Children's Health Act, this is a "national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development." Because, as previously mentioned, children are especially vulnerable to a wide array of environmental exposures, the study will focus on the interactions of biologic, genetic, social and other factors to better understand their role in the origin of disease and to increase the understanding of health disparities. The study will include approximately 100,000 children across the U.S., identified early in pregnancy and followed through birth and childhood, and into adulthood. At present, 22 working groups are developing the specifics of this far-ranging study, and we are working with our federal partners to fund the pilot studies needed.

The NIEHS is also exploring partnerships with the U.S. Geological Survey (USGS) to see if existing exposure-related data could be used by environmental health scientists. One outgrowth of this collaboration could be an online data and information clearinghouse

capability through which environmental health researchers could quickly locate existing exposure data sets and other relevant information. Both the NIEHS and the USGS are enthusiastic about this project. Our next meeting will be in April and we hope through our efforts to design a "gold standard" for the sort of exposure data and clearinghouse that could be most useful to environmental health scientists.

NATIONAL OR HOMELAND SECURITY

The other area in which NIEHS has expertise, and can be expected to contribute, is in the Nation's preparation to prevent toxicity and death from bioterrorism. The potential use of biological or chemical weapons by terrorists is a serious threat to human health. Such weapons are capable of causing extraordinary devastation. We need technologies capable of detecting, tracking, and containing chemical poisons or infectious microorganisms. The gene and protein expression technologies being developed in our National Toxicogenomic Center can be used to track exposure and predict toxicity. To cause tissue damage, chemicals and infectious agents must modulate gene expression and/or protein function. Identification of such genes and characterization of their function can provide importance clues for understanding, and ultimately preventing, the progression of the disease. The specific pattern of gene response can also provide clues about host defense mechanisms which can also be exploited for prevention. Also, one can use this technology to identify virulence genes (i.e., genes whose expressions are critical for the pathogen to overcome body or host defense mechanisms).

Over the past 35 years, the NIEHS has developed a cadre of first-rate researchers in the environmental health sciences. More than 100 of these researchers are affiliated with five NIEHS-supported Centers in the New York area. They are among the best environmental health research scientists in the world, with expertise in air pollution, asbestos toxicity, exposure assessment, children's health, and population-based epidemiology studies. Because of their leadership and national visibility, many of them were contacted by city and state officials to engage them in health assessment and environmental remediation decisions following the attack on the World Trade Center (WTC). These investigators have access to technological resources, and have the experience necessary to manage environmental health threats posed by the WTC disaster. Since September 11, they have initiated research activities with NIEHS support and coordination. Their efforts include exposure assessment, epidemiology, medical care and clinical evaluation, and community outreach and education. These activities are now being integrated into the government-wide effort coordinated by the Federal Emergency Management Agency.

Finally, NIEHS can use the National Toxicology Program to conduct toxicological evaluations of defined mixtures of contaminants identified by environmental monitoring studies of ambient and indoor air and dust; and, to evaluate the safety of therapeutic regimens and intervention measures likely to be employed in biological or chemical terrorism events.

SUMMARY

Environmental health prevention research helps eliminate the epidemic of disease. Investment in such research saves lives, spares pain and suffering, and saves money in the years ahead. The proposed and ongoing research will lead to more-effective environmental surveillance systems with the capacity to rapidly analyze and assess the health risks of chemical and biological agents. Toxicogenomics is potentially a toolbox of powerful technologies to determine how chemicals and infectious microorganisms cause illness and death.

At this time, I would be happy to answer any questions you might have.